Screening for content—the evolution of high throughput

Alan Dove

Despite a poor return on investment thus far, innovations in high-throughput screening are still very much in demand.

According to legend, Thomas Huxley once argued that a room full of monkeys pounding on typewriters would eventually produce Shakespeare's *Hamlet*. Over the past decade, pharmaceutical companies have tried an analogous approach to developing new drugs, semirandomly synthesizing millions of distinct chemical compounds, then screening them for the next blockbuster. But just as keyboard-equipped primates display only rare flashes of brilliance, the advent of high-throughput screening has so far done little to bolster shriveling drug development pipelines. Indeed, the advent of high-throughput screening has coincided with a dearth of drugs; the past few years have seen a precipitous drop in new drug approvals (see **Fig. 1a**).

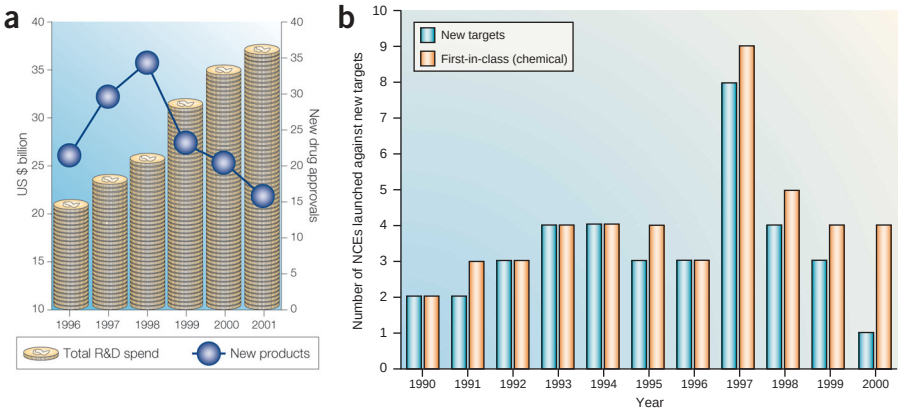

Figure 1 Waning drug approvals. (a) R&D spending versus new drug launches. Reprinted with permission from *Nature* (**418**, 453, 2002). (**b**) Small-molecule, 'first-in-class' drugs and associated new drug targets launched in the past decade. Reprinted with permission from *Nature Reviews Drug Discovery* (**1**, 727, 2002).

From high throughput to high content

In principle, high-throughput screening sounds very straightforward. Combinatorial chemists arrange a set of chemical building blocks into all possible combinations, generating a library of millions of compounds. These are then fed into an automated screening system, often patterned onto silicon chips, to determine which compounds bind to a particular target protein or inhibit a particular enzymatic reaction. The successful compounds, now called 'hits', then enter secondary screens to check a number of parameters, including toxicity to cells, solubility and reactivity with nontarget cellular proteins. The chemicals that pass the secondary screens, dubbed 'leads', are then tested in progressively more complex systems, from cells to whole animals, before reaching clinical trials.

Alan Dove is a Contributing Writer at Nature Biotechnology.

Although screening technologies have evolved in recent years, some observers are starting to wonder when—or whether—this strategy will pay off. Indeed, high-throughput screening has done little to remedy the current dearth of drugs, as the numbers of new drugs and targets shrink (see **Fig. 1**). The guiding philosophy of high-throughput screening is to fail early, eliminating unpromising compounds before they reach the expensive end of the drug development pipeline. Unfortunately, despite ever-increasing rates of throughput, promising leads continue to fail in costly animal studies and even costlier clinical trials, and high-throughput screening has yet to yield a blockbuster.

However, it would be premature to plan a funeral for such a young field. Dozens of small and medium-size biotechnology companies—and all of the pharmaceutical giants—are enthusiastically embracing a set of new technologies that they hope will allow high-throughput screening to realize its potential. Indeed, the numbers of biotech-pharma alliances involving high-throughput screening continues to grow (see **Fig. 2**), though not at the rate it was increasing in the 1990s. However, rather than just testing more compounds with brute-force automation, new approaches, loosely referred to as 'high-content screening', rely on sophisticated assays and algorithms to increase the chances of finding successful drugs.

Originally coined with a specific meaning in mind, the term 'high-content screening' has evolved into the latest biotech buzzword. Like 'proteomics' before it, 'high content' is now being applied to a wide range of vaguely related activities—from single-cell assays to cell sorting. As with previous buzzwords, the industry will eventually have to develop its own working definition. For now, most experts in high-throughput screening prefer to restrict the term 'high content' to automated assays

Box 1 An abundance of assays

Recent advances in basic cell biology have been a boon to biotechnology and pharmaceutical companies searching for better assays to screen potential drugs. Whereas a few 'legacy' assays left over from earlier studies still rely on radioactive labeling, most screening efforts have switched to more sensitive and flexible fluorescent markers.

Unlike radioactive labels, which usually produce simple black spots on X-ray film, fluorescent labels are available in an array of colors and can be viewed in a variety of ways. Fixed cells can be stained with fluorescently tagged antibodies to show not only the presence or absence of a particular protein form, for example a phosphorylated signaling molecule, but also its localization within the cell. Using a different fluorescent tag on each antibody, such an assay can show the simultaneous states and positions of multiple proteins, providing detailed information about the physiological state of the cell.

Whereas some assays with antibodies can only be done on fixed cells, the green fluorescent protein (GFP) from the ctenophore *Aequoria victoria* glows brightly inside living cells, making it possible to study many intracellular processes in real time. Scientists can attach GFP coding sequences to a gene of interest, then use time-lapse video and imaging software to track its whereabouts. Recent modifications of this system also allow multicolored staining, and GFP is now the basis of several companies' high-content screening systems.

Besides these technical advances, cell biologists have uncovered a wealth of information about cell physiology, leading to faster, simpler assays. By monitoring a few key signaling molecules, for example, researchers can determine whether a cell is undergoing apoptosis, or programmed cell death, a common response to toxic compounds. Similarly, research on cell proliferation and motility is permitting new assays for drugs that might inhibit tumor growth and metastasis.

Whether these assays are used in transformed cell lines, primary cell cultures or whole animals, companies hope that the new technologies will provide not only greater speed and efficiency, but also increased biological relevance, a key requirement in the fail-early philosophy of high-throughput screening. *AD*

that measure multiple parameters of individual cells within wells or plates.

Although a large number of companies claim to be doing high-content screening, the field divides easily into drug development companies and tool companies (see **Tables 1** and **2** for a partial list), There has traditionally been some overlap between the two; tool companies may do some drug screening of their own, and drug developers may design some of their own assays. But recent belt-tightening has encouraged biotechnology companies to emphasize one business plan or the other. Profiling a sample of both types of companies shows that as the field struggles to prove itself, each strategy presents its own risks and rewards.

Keeping the hits coming

In the 1990s, rapid progress in combinatorial chemistry and protein biochemistry inspired a drive for ever higher throughput, in the hope that simply conducting more assays per day would yield better results. Although this trend generated some undeniably clever technological breakthroughs in miniaturization and automation[1], it did not put more drugs into the pipeline. As a result, "the pharmaceutical industry has shifted their thinking from 'let's get as large a compound library as possible and run as many assays as fast as we can,' to a more focused screening mentality," according to Lansing Taylor, CEO of Cellomics (Pittsburgh, PA, USA).

This shift has led many companies to concentrate more on cell-based functional assays, which have the potential to yield more information than assays in homogeneous solutions. Cultured cells are more biologically relevant than isolated proteins, but they have some major drawbacks. Even a small screening program may involve hundreds of thousands of drug candidates, and traditional cell culture techniques are time-consuming, expensive and difficult to handle at that scale.

Miniaturization has helped, reducing cell culture volumes to as little as a few microliters on a 3,456-well plate, but each well still represents a population of cells that might not be entirely homogeneous. Worse, living biological systems are notoriously unreliable, so multiple controls are required to be sure that an assay result is real.

To address these problems, Cellomics (who claim to have coined 'high-content screening') developed a set of technologies for analyzing individual cells and subcellular processes in automated readers. The data can include simultaneous measurements of several physiological parameters in each cell, making them much more complex but also more informative than simpler readouts from primary screens (see **Box 1**).

"You're looking at the effect of the compound not only on the target, but if you can look at cytotoxicity in parallel to that and also ask questions about the impact on cell physiological events or other targets, you can use cell-based assays to fail compounds earlier," says Taylor.

Although Cellomics provides the tools for biologically relevant functional assays, drug developers must still decide which proteins or pathways they wish to target. The flood of new potential targets pouring out of genome-sequencing projects presents an enormous opportunity, but also makes this choice more difficult. In response, researchers at Akceli (Medford, MA, USA) are turning high-throughput screening on its head, developing methods to screen relatively small numbers of compounds against large libraries of targets.

Akceli's key technology, called reverse transfection, based on the work of David Sabatini at The Whitehead (Cambridge, MA, USA), involves plating a hydrogel containing a plasmid and a transfecting agent onto a tiny spot of a culture plate. Cells on that spot then take up only that plasmid, whereas neighboring cells on a different spot take up a different plasmid. The result is that a single well of a 96-well microtiter plate can contain up to 36 spots of cells expressing different drug targets. Working this way, one system expresses all of the tyrosine kinases in the human genome in just four wells of a microtiter plate. A standard plate reader and imaging software can then interpret the responses of all of the kinases to a given drug, producing a detailed profile of the drug's selectivity (see **Fig. 3**).

David Chao, president and founder of Akceli, expects that the technology will initially be used "where people have very focused libraries ... and screen a small number of compounds, say 10,000, against a small number of targets, say 100. It's also great for understanding the mechanism of action of existing drugs." Besides tyrosine kinases, Akceli is also developing systems to profile the responses of G-protein-coupled receptors, critical mediators of many types of intercellular signals.

In addition to small biotechnology companies, large laboratory suppliers are also developing high-content screening technologies. Amersham Biosciences (Piscataway, NJ, USA), for example, now offers two integrated cell-based screening systems, the IN Cell 1000 and IN Cell 3000. Like Cellomics, Amersham is focusing on analyzing individual cells within microtiter plates, using fluorescent reporter

genes to take multiple measures of cellular health. The IN Cell 1000 is designed as a laboratory-scale version of the larger IN Cell 3000, allowing companies to develop new assays and then scale them up with minimal alteration.

Ger Brophy, vice president of business development for Amersham, predicts that cell-based screening will also move farther back in the pipeline: "The position of this technology for the next couple of years will be at the secondary stage, but I do believe that increasingly people will try to do more cell analysis in primary screening. That will allow them to ask more penetrating questions at the stage of hit development."

Indeed, for large pharmaceutical companies, Brophy's prediction is already coming true. "For our screening, a large part of our assays are cell-based, so rather than become the ternary assay, now cell-based assays are becoming the primary assay," says Berta Strulovici, executive director of automated biotechnology at Merck Research Laboratories (West Point, PA, USA).

Fishing for leads

Even with good secondary screens, a high-throughput screening program can rapidly produce hundreds of promising-looking leads, most of which will fail in animal tests. Large rodent colonies are expensive to maintain, inspiring many companies to seek cheaper animal systems that can still provide physiologically relevant information. Two longtime laboratory favorites, the worm *Caenorhabditis elegans* and the fruit fly *Drosophila melanogaster*, have recently been

Table 1 Selected companies specializing in high-throughput cell-based screening

Company	Technology/service	Partner
Acadia Pharmaceuticals (San Diego, CA, USA)	Receptor Selection and Amplification Technology: Amplifies mammalian cell lines that carry marker gene/targets that respond to a test compound.	Allergan (Irvine, CA, USA) Amgen (Thousand Oaks, CA, USA)
Akceli (Medford, MA, USA)	Microarrays of mammalian cells each transfected with a different plasmid encoding a potential drug target.	
Athersys (Cleveland, OH, USA)	Random Activation of Gene Expression: Library of cultured mammalian genome each expressing an individual gene, created by the random insertion of a vector with an on-signal and a tag for isolating the gene product.	Pfizer (New York, NY, USA) Bristol-Meyers Squibb (Princeton, NJ, USA) Medarex (Princeton, NJ, USA) Acorda Therapeutics (Hawthorne, NY, USA)
Bioseek (Burlingame, CA, USA)	Primary human (endothelial, epithelial and lymphocyte) cells modulated with drugs, cytokines, or genetically altered to model disease or identify drug responses and pinpoint new targets for existing compounds using protein readouts.	Dynavax (Emeryville, CA, USA)
Bionaut Pharmaceuticals (Cambridge, MA, USA)	Sentinel Cell Lines: mammalian cell lines (primary, cancer and established cell lines) expressing reporter genes that respond to signaling molecules (epidermal growth factor, tumor necrosis factor) and ligands.	AstraZeneca (Wilmington, DE, USA) Biogen (Cambridge, MA, USA)
Cytokinetics (S. San Francisco, CA, USA)	PUMA: multiprotein biochemical screens for inhibitors or kinesin molecular motors; Cytometrix: automated cellular phenotyping imaging/informatics	GlaxoSmith Kline (Brentford, UK) Exelixis
Exelixis (S. San Francisco, CA, USA)	Model systems combined with cell-based assays—stable cell lines overexpressing drug targets.	Bristol-Meyers Squibb, SmithKline Beecham, Protein Design Labs (Freemont, CA, USA), Cytokinetics (S. San Francisco, CA, USA), Elan Pharmaceuticals (Dublin, Ireland), Merck (Whitehouse Station, NJ, USA), Scios (Sunnyvale, CA, USA), Schering-Plough (Madison, NJ, USA),Bayer (Leverkusen, Germany), Dow (Midland, MI, USA), Renessen (Bannockburn, IL, USA)
Odyssey Thera (San Ramon, CA, USA)	Protein-fragment complementation assay: fluorescence-based assay for detecting drugs that interfere with protein interactions *in vivo*.	Incyte (Palo Alto, CA, USA)
Psychiatric Genomics (Gaithersburg, MD, USA)	Multi-Parameter High-Throughput Screen (MPHTSSM). uses postmortem brain to identify disease signature and neuronal cell cultures to identify drug signatures.	Evotec OAI (Hamburg, Germany), ReNeuron (Gaithersburg, MD, USA)
Rigel (S. San Francisco, CA, USA)	Retroviral probes and two-hybrid screening in yeast for target identification combinatorial biology to design functional screens for target validation.	Pfizer, Novartis (Basel, Switzerland), Johnson&Johnson (New Brunswick, NJ, USA)
Vertex (Cambridge, MA, USA)	Aurora cell-based ion channel and β-lactamase reporting systems combined with family-based drug discovery	Novartis
Xantos Biomedicine (Martinsreid, Germany)	XantoScreen: transfects genes into and observes consequent phenotypic changes in disease-relevant human cells.	F. Hoffman-LaRoche (Nutley, NJ, USA)

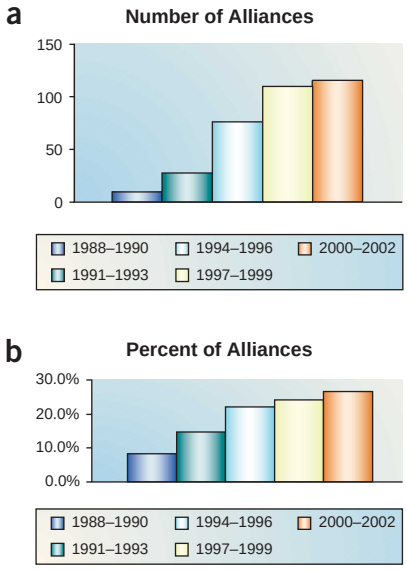

Figure 2 High throughput screening alliances. (a) Number of biotech alliances focusing on screening technology with top 20 pharma companies. (b) Screening alliances as a percentage of all biotechnology alliances. Source: Recombinant Capital

Box 2 Virtual screening

As originally conceived, high-throughput screening aimed to test as many compounds as possible, letting assays eliminate unpromising leads. More recently, scientists have started focusing on winnowing the field even before screening begins, using computer algorithms to eliminate compounds from combinatorial libraries.

"To some extent, you can look at the historical trends of compounds that have made it, and there are some rules one can identify within that set," explains Paul Negulescu, vice president of discovery biology at Vertex Pharmaceuticals (Cambridge, MA, USA). Vertex applies these rules through a set of algorithms called Rapid Elimination of Swill (REOS). The system correlates particular molecular features with specific liabilities, reducing the chance that a promising lead will turn out to be insoluble or highly toxic, for example. Other companies, including most large pharmaceutical firms, have developed similar algorithms.

Of course, there is some risk of throwing out good drugs. "Doing everything *in silico* I think is not the way to go, you've got to balance that with actual experimentation to modify your hypotheses," says Negulescu.

Even with sophisticated algorithms, though, not everyone is sold on the idea of computer-based screening. "I would consider that approach a shortcut. We believe that the process of high-throughput screening has to have an element of serendipity, which is eliminated by knowing in advance what you're going to screen," says Berta Strulovici, executive director of automated biotechnology at Merck Research Laboratories (West Point, PA, USA). *AD*

joined by the zebrafish, *Danio rerio*, in screening labs.

It is difficult to beat the high-throughput possibilities of *C. elegans*, which can be reared by the millions in simple culture plates, and the well-characterized genetics of the fruit fly make it useful for analyzing mutagenic compounds. For physiological relevance, though, fish swim to the head of the school.

"We are using zebrafish for toxicological screening, developmental toxicology, teratogenicity, and organ-specific assays, like looking at liver and seeing what drugs are doing to it," says Chaoyong Ma, business development manager at Phylonix (Cambridge, MA, USA). Besides being much cheaper to raise and maintain than rodents, zebrafish develop inside a

Table 2 Selected companies specializing in supplying equipment, chemicals and reagents for high-throughput cell screening

Company	Product
Acumen Biosciences (Royston, UK)	Explorer: laser scanner for cell-based screens
Amersham Biosciences (Piscataway, NJ, USA)	IN Cell Analyzer 1000/3000 multiparameter, laser-based cellular imaging system
The Automation Partnership (Cambridge, UK)	SelectT: fully automated batch cell culture
Cellomics (Pittsburgh, PA, USA)	ArrayScan:. high-throughput cell screening system, fluorescent reagents and assays, co-marketed with Carl Zeiss Ultra High Throughput Screening system
Evotec OAI (Abingdon, UK; Hamburg, Germany)	EVOscreen-miniaturized assays, single-molecule fluorescence-based detection
Gene Data (Basel, Switzerland)	Integrated software program for visualization and analysis of high-throughput screening and compound profiling data
Molecular Devices (Sunnyvale, CA, USA)	Discovery-1: visualize and analyze cell populations. Discovery TMA: for tissue microarrays, FLIPR: fluorescence imaging plate reader
PE Biosystems (Boston, MA, USA)	ImageTrak: epifluorescence cell imaging
Phylonix (Cambridge, MA, USA)	*In vivo* zebrafish assays
Q3DM (San Diego, CA, USA)	High-throughput microscopy and cell imaging instrumentation
Union Biometrica (Somerville, MA)	High-throughput analysis sorting and dispensing of multicellular organisms
Universal Imaging (Downington, PA, USA)	MetaMorph High-Content Screening Software
VitraBioscience (Sunnyvale, CA, USA)	CellCard: dispensing, imaging and analysis system for adherent cells CellPlex assays: multiparametric analysis of multiple cell types in a well

transparent egg, allowing Phylonix researchers to use a wide range of visual screens and fluorescent labeling techniques in their assays (see Fig. 4).

Zebrafish embryos are also small, so they can be distributed into 96-well plates for relatively rapid analysis. In addition to toxicology, Phylonix can quantify a drug's effects on angiogenesis, apoptosis and heart rate.

While Phylonix is developing assays in fish, nearby Union Biometrica (Somerville, MA, USA) is scaling up the system. "Any kind of analysis that you're going to do, you have to keep in mind you're going to be moving [fish] one at a time. What we bring to the table is the opportunity to ... start thinking of bigger scale experiments in these models." Using its proprietary complex object parametric analyzer and sorter (COPAS), Union Biometrica can now handle zebrafish embryos in 15,000-well sets, allowing them to examine up to 50,000 fish per day. COPAS can also handle even larger numbers of flies or worms.

Nor is the sorting limited to simple positive or negative assays. The company is now refining imaging software that allows it to separate fish embryos on the basis of virtually any phenotype that can be measured optically. In addition to identifying varying levels of fluorescent protein expression, the system may be able to detect anatomical defects that a drug induces during development.

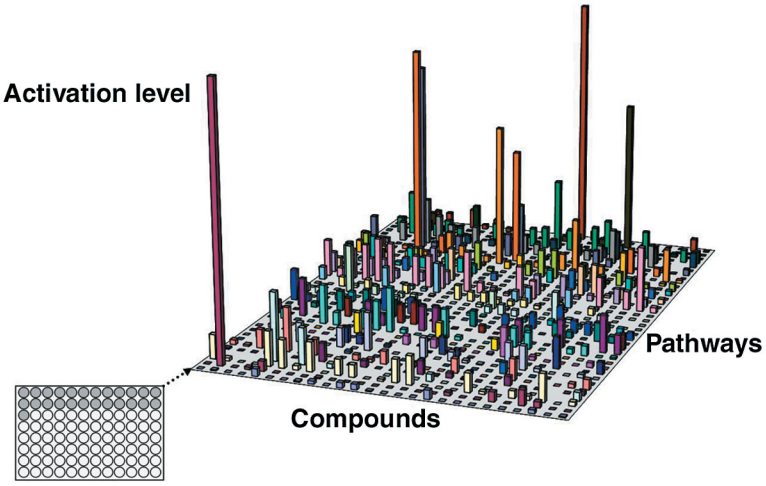

Figure 3 A 900-data point profile with Akceli cell microarrays. Plasmids generating readouts for 35 different pathways are printed as microarrays in each of 35 wells. After cells are applied to each well under conditions where the plasmids are transfected and expressed, 25 different compounds are added, and their effect is then assayed. (Image courtesy of Akceli.)

The jury remains out

The new high-content screening technologies are certainly promising, but as the history of the field demonstrates, it takes more than a nice assay to develop a successful drug. Paul Negulescu, vice president of discovery biology at Vertex Pharmaceuticals (Cambridge, MA, USA), says that companies doing high-throughput screening "have moderated their expectations with respect to throughput and have moderated their expectations with respect to biology, and they've also improved their starting compounds."

In addition to streamlining the screening process, companies like Vertex are trying to make their combinatorial libraries leaner with new computational strategies (see **Box 2**). The enduring slump in biotechnology funding has driven some of these changes; Vertex, for example, announced in June that it would be restructuring and laying off more than 100 employees.

In the wake of the cuts, the company "narrowed the number of targets, and is also looking only at areas of highest therapeutic interest now," according to Negulescu. Despite the bad news, Vertex has now moved three of its lead compounds into formal preclinical trials, bringing high-throughput screening one step closer to a success story.

Besides just getting compounds into animal systems, Vertex is hoping to make high-throughput screening a more predictive

Table 3 Screening casualties

Company	Fate
3-D Pharmaceuticals (Yardley, PA, USA)	Acquired by Johnson&Johnson in March 2003
Alanex (La Jolla, CA, USA)	Acquired by Agouron (La Jolla, CA, USA) in April 1997 (now part of Pfizer)
Aurora Biosciences (San Diego, CA, USA)	Acquired by Vertex in April 2001
Axys Advanced Technologies (San Diego, CA, USA)	Merged with Drug Discovery Partner (San Diego, CA, USA) in April 2000
Axiom Biotechnologies (San Diego, CA, USA)	Acquired by Sequenom (San Diego, CA, USA) in August 2002
Biometric Imaging (Mountain View, CA, USA)	Acquired by Becton Dickinson (Franklin Lakes, NJ, USA) in February 1999
Cadus Pharmaceutical (Cambridge, MA, USA)	Sold discovery programs to OSI Pharmaceuticals in July 1999 and changed business
CombiChem (San Diego, CA, USA)	Acquired by Deltagen (from Bristol-Meyers) in February 2002
EG&G Wallac (Gaithersburg, MD, USA)	Acquired by Perkin Elmer (Norwalk, CT, USA) in 1998
LJL Biosystems (Sunnyvale, CA, USA)	Acquired by Molecular Devices (Sunnyvale, CA, USA) in June 2000
Packard Bioscience (Meridan, CT, USA)	Acquired by Perkin Elmer in November 2001
Scriptgen Pharmaceuticals (Waltham, MA, USA)	Merged with Asklipios to form Anadys (San Diego, CA, USA) in May 2000
Zymark (Hopkinton, MA, USA)	Acquired by Caliper (Hopkinton, MA, USA) in June 2003

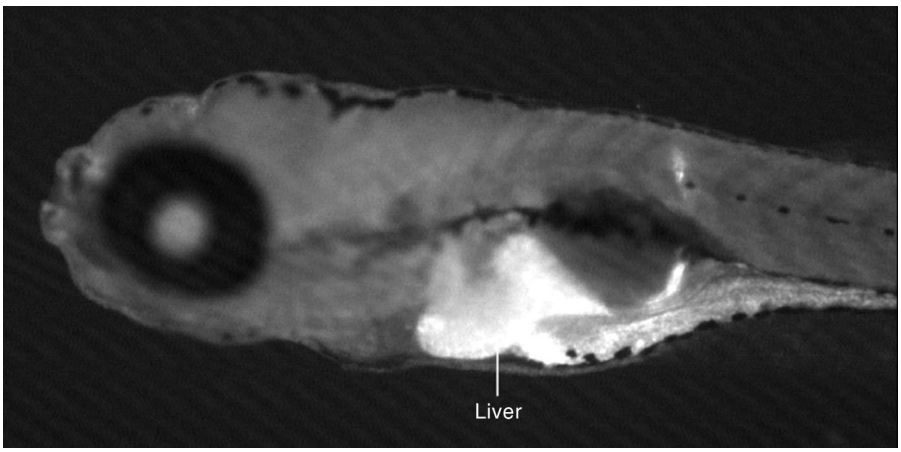

Figure 4 Avidin-rhodamine staining of liver of an intact zebrafish embryo. Because these embryos are transparent, fluorescent staining allows researchers to perform detailed studies on the toxicity and efficacy of lead compounds before testing them in rodents. (Image courtesy Phylonix.)

process. On the basis of the results of their cell-based screens, the company made specific predictions about how particular compounds would act in animals. So far, at least in a few animal studies, the lead compounds are behaving exactly as expected, suggesting that the cell-based assay has achieved true biological relevance. According to Negulescu, Vertex is "optimistic that these approaches are going to pay off in the near term by allowing us to focus on the appropriate molecules as early as possible."

Like Vertex, Rigel (S. San Francisco, CA, USA) is using the new technologies to develop its own pipeline of drugs. "We're one of the few companies that has taken functional genomics technologies and actually put products into the clinic," says Raul Rodriguez, Rigel's senior vice president of business development. The company's small-molecule drug for allergic rhinitis is in phase 1 trials now, and its drugs for hepatitis C and rheumatoid arthritis are expected to enter phase 1 by early next year.

Rigel's approach to new screening technologies is fairly typical: "We'll buy various components and then basically break them down and rebuild according to our mission. Then of course the database software has to be customized for the questions. Unfortunately, I think that's where the off-the-shelf stuff doesn't cut it," says Don Payan, the company's chief scientific officer.

Box 3 High-content financing

The continuing drought in biotechnology funding has not spared companies focused on high-content screening, and the field continues to see its share of reorganizations, acquisitions and outright failures (see **Table 3**). "A lot of companies got started around a unique technology or niche, and haven't been able to execute the transition to companies that can sell products," says Don Payan, chief scientific officer for Rigel (S. San Francisco, CA, USA).

In contrast to the heady days of the late 1990s, investors now ask what a company will be able to sell, and to whom. Rigel, for example, initially described itself as a functional genomics company, but found that term was unattractive to investors, because functional genomics "has not been successful in putting things in the clinic," according to Payan. Describing itself as a drug development firm—and getting lead compounds into clinical trials—has substantially improved the company's financing.

Rigel's evolving strategy is not unusual, but other companies have chosen to concentrate on technology development rather than seeking their own drugs. "When the landscape for venture capital changed, [some technology companies] also focused on drug development, since that was more amenable to funding," says Ger Brophy, vice president of business development at Amersham Biosciences (Piscataway, NJ, USA), but "being a large technology provider, we have not had a need to change our business model."

Smaller companies have also found the tool business worthwhile. "We currently don't have plans to develop drugs internally. We are focused on providing services to other companies," says Chaoyong Ma, business development manager for Phylonix (Cambridge, MA, USA). Amply funded with grants and customer contracts, Phylonix has not needed to chase scarce venture capital in recent years.

Nonetheless, technology companies face a complex set of challenges trickling down through the industry. "The rate of spending, especially on capital equipment, has slowed and the sales cycle has lengthened …so it's filtered down to the business models and business practices of the biotechs," says Lansing Taylor, CEO of Cellomics (Pittsburgh, PA, USA). Like Amersham and Phylonix, Cellomics stuck with its core technologies, but it has had to sacrifice longer-term projects to survive. *AD*

Looking ahead

Because most pharmaceutical companies tend to combine in-house and purchased technologies, firms that focus on developing those technologies will have to be flexible to survive (see **Box 3** and **Table 3**). "We're not precious enough to believe that we always have all the answers, so we're very careful to ensure that our systems are modular," says Amersham's Brophy. Even though the company sells integrated screening systems, many of its customers still prefer to combine parts of the machines with components from other vendors.

Although many biotechnology companies are actively engaged in high-throughput screening, the biggest pharmaceutical companies will likely retain an edge. Even with innovative tools, this is a field where size still matters, especially when shopping for new technologies. "We look all the time at what's out there, and when there is something new, we always try it, and if it works we propose it to management, and usually get backup if it's something that's sound," says Merck's Strulovici. Relying heavily on miniaturization and cell-based assays, Merck is currently screening large libraries of compounds, primarily in 1,536- and 3,456-well plates.

Even optimistic observers agree that it will be several more years before high-throughput screening and its offspring, high-content screening, start to pay dividends, but the combination of new scientific approaches and sound business strategies is giving the field its best chance for success. In essence, the room is being staffed with smarter monkeys, but only time will tell whether they succeed as playwrights.

1. Dove, A. Drug screening—beyond the bottleneck. *Nat. Biotechnol.* **17**, 859–863 (1999).